

## CLAIMS

1. A polyvalent protein complex (PPC) comprising a first and a second polypeptide chain,

wherein said first polypeptide chain comprises a polypeptide sequence represented, by the formula  $a_1-l_1-a_2-l_2-a_3$ ,

wherein  $a_1$ ,  $a_2$ , and  $a_3$  are immunoglobulin variable domains and  $l_1$  and  $l_2$  are peptide linkers, and  $a_1$  is N-terminal of  $a_2$ , which in turn is N-terminal of  $a_3$ ,

wherein said second polypeptide chain comprises a polypeptide sequence represented by the formula  $b_1-l_3-b_2-l_4-b_3$ ,

wherein  $b_1$ ,  $b_2$ , and  $b_3$  are immunoglobulin variable domains and  $l_3$  and  $l_4$  are peptide linkers, and  $b_3$  is N-terminal of  $b_2$ , which in turn is N-terminal of  $b_1$ ,

wherein said first and second polypeptide chain together form a complex comprising at least three antigen binding sites,

wherein each of said antigen binding sites comprises a variable domain from said first polypeptide chain and a variable domain from said second polypeptide chain, and

wherein each binding site comprises an immunoglobulin heavy chain variable domain and an immunoglobulin light chain variable domain.

2. The complex according to claim 1 wherein each polypeptide chain further comprises 1-3 additional immunoglobulin variable domains, wherein each domain is linked via a peptide linker,

wherein said first and second polypeptide chain together form a complex comprising 4-6 antigen binding sites, and

wherein each of said antigen binding sites comprises a variable domain from said first polypeptide chain and a variable domain from said second polypeptide chain.

3. The complex according to claim 1, wherein at least one polypeptide chain further comprises an amino acid sequence selected from the group consisting of a toxin, a cytokine, a lymphokine, an enzyme, a growth factor, and an affinity purification tag.

4. The complex according to claim 1, wherein at least two of said antigen binding sites have the same binding specificity.

5. The complex according to claim 1, wherein each of said antigen binding sites has a different binding specificity.

6. The complex according to claim 4, wherein said antigen binding sites have the same binding specificity.

7. The complex according to claim 2 wherein said antigen binding sites have at least two different binding specificities.

8. The complex according to claim 7 wherein at least 3 of said antigen binding sites have different binding specificities.

9. The polyvalent protein complex of claim 7 wherein at least 4 of said antigen binding sites have different binding specificities.

10. The complex according to claim 7 comprising at least 5 antigen binding sites wherein at least 5 of said binding sites have different binding specificities.

11. The complex according to claim 7 comprising 6 antigen binding sites each having a different binding specificity.

12. The complex according to claim 7 comprising at least 5 antigen binding sites wherein at least 5 of said binding sites have different binding specificities.

13. The complex according to claim 1, wherein two of said antigen binding sites are specific for epitopes of tumor associated antigens, and wherein said third antigen binding sites is reactive with a targetable construct .

14. The polyvalent protein complex of claim 13, wherein two antigen binding sites are specific for epitopes of tumor associated antigens, and wherein the third antigen binding sites is reactive with a targetable construct, and wherein the epitope on the targetable construct is a hapten.

15. A complex comprising at least one complex according to claim 1 bound to a targetable construct, wherein said complex is bound to a first hapten on said construct and wherein said construct further comprises a second hapten capable of binding simultaneously to a second polyvalent protein complex.

16. The polyvalent protein complex of claim 14, wherein the tumor associated antigen, or antigens are selected from the group consisting of antigens associated with carcinomas, melanomas, sarcomas, gliomas, leukemias and lymphomas.

17. The polyvalent protein complex of claim 14, wherein the tumor associated antigen is selected from the group consisting of  $\alpha$ -fetoprotein, A3, CA125, carcinoembryonic antigen (CEA), CD19, CD20, CD21, CD22, CD23, CD30, CD33, CD45, CD74, CD80, colon-specific antigen-p (CSAp), EGFR, EGP-1, EGP-2, folate receptor, HER2/neu, HLA-DR, human chorionic gonadotropin, Ia, IL-2, IL-6, insulin-like growth factor, KS-1, Le(y), MAGE, MUC1, MUC2, MUC3, MUC4, NCA66, necrosis antigens, PAM-4, placental growth factor, prostatic acid phosphatase PSA, PSMA, S100, T101, TAC, TAG-72, tenascin and VEGF.

18. The polyvalent protein complex of claim 16, comprising at least two tumor antigen binding sites, wherein both tumor antigen binding sites are specific for CEA and wherein the third binding site is specific for the hapten, histamine-succinyl-glycine (HSG).

19. The polyvalent protein complex of claim 16, wherein the polyvalent protein is BS14HP, or hBS14.

20. A complex comprising a polyvalent protein complex according to claim 19, bound to IMP 241, or IMP 245

21. A pretargeting method of treating or diagnosing or treating and diagnosing a neoplastic condition comprising

(a) administering to said subject the polyvalent protein complex of claim 1, wherein two antigen binding sites are directed to a tumor associated antigen, and one antigen binding sites is directed to a targetable construct comprising a bivalent hapten;

(b) optionally, administering to said subject a clearing composition, and allowing said composition to clear the polyvalent complex from circulation; and

(c) administering to said subject said targetable construct comprising a bivalent hapten, wherein said targetable construct further comprises one or more chelated or chemically bound therapeutic or diagnostic agents.

22. The method of claim 21, wherein the diagnostic agent is a radionuclide selected from the group consisting of  $^{18}\text{F}$ ,  $^{52}\text{Fe}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{86}\text{Y}$ ,  $^{89}\text{Zr}$ ,  $^{94\text{m}}\text{Tc}$ ,  $^{94}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{154-158}\text{Gd}$ ,  $^{177}\text{Lu}$ ,  $^{32}\text{P}$ ,  $^{188}\text{Re}$ , and  $^{90}\text{Y}$  or a combination thereof.

23. The method of claim 22, wherein said radioactive labels are imaged using computed tomography (CT), single photon emission computed tomography (SPECT), or positron emission tomography (PET).

24. The method of claim 22, wherein the application is for intraoperative diagnosis to identify occult neoplastic tumors.

25. The method of claim 21, wherein said targetable construct comprises one or more image enhancing agents for use in magnetic resonance imaging (MRI).

26. The method of claim 25, wherein said image enhancing agent is a metal selected from the group consisting of chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), vanadium (II), terbium (III), dysprosium (III), holmium (III) and erbium (III).

27. The method of claim 21, wherein said targetable construct comprises one or more image enhancing agents for use in ultrasound imaging.

28. The method of claim 21, wherein said targetable construct is a liposome with a bivalent HSG-peptide covalently attached to the outside surface of the liposome lipid membrane.

29. The method of claim 28, wherein said liposome is gas filled.

30. The method of claim 21, wherein said targetable construct comprises one or more radioactive isotopes useful for killing neoplastic cells.

31. The method of claim 30, wherein said radioactive isotope is selected from the group consisting of  $^{32}\text{P}$ ,  $^{33}\text{P}$ ,  $^{47}\text{Sc}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{67}\text{Ga}$ ,  $^{90}\text{Y}$ ,  $^{111}\text{Ag}$ ,  $^{111}\text{In}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{142}\text{Pr}$ ,  $^{153}\text{Sm}$ ,  $^{161}\text{Tb}$ ,  $^{166}\text{Dy}$ ,  $^{166}\text{Ho}$ ,  $^{177}\text{Lu}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{189}\text{Re}$ ,  $^{212}\text{Pb}$ ,  $^{212}\text{Bi}$ ,  $^{213}\text{Bi}$ ,  $^{211}\text{At}$ ,  $^{223}\text{Ra}$  and  $^{225}\text{Ac}$  or a combination thereof.

32. The method of claim 30, wherein the pretargeted therapy is administered prior to, with or after one or more therapeutic agents.

33. The method of claim 32, wherein said therapeutic agent is a cytokine or a chemotherapeutic agent, or a colony-stimulating growth factor.

34. The method of claim 33, wherein said therapeutic agent is a chemotherapeutic agent selected from the group consisting of taxanes, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas, triazenes; folic acid analogs, pyrimidine analogs, purine analogs, vinca alkaloids, antibiotics; enzymes, platinum coordination complexes, substituted urea, methyl hydrazine derivatives, adrenocortical suppressants, and antagonists.

35. The method of claim 33, wherein said therapeutic agent is a chemotherapeutic agent selected from the group consisting of steroids, progestins, estrogens, antiestrogens, and androgens.

36. The method of claim 33, wherein said therapeutic agent is a chemotherapeutic agent selected from the group consisting of azaribine, bleomycin, bryostatin-1, busulfan, carmustine, chlorambucil, cisplatin, CPT-11, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone, diethylstilbestrol, doxorubicin, ethinyl estradiol, etoposide, fluorouracil, fluoxymesterone, gemcitabine, hydroxyprogesterone caproate, hydroxyurea, L-asparaginase, leucovorin, lomustine, mechlorethamine, medroprogesterone acetate, megestrol acetate, melphalan, mercaptopurine, methotrexate, methotrexate, mithramycin, mitomycin, mitotane, phenyl butyrate, prednisone, procarbazine, semustine streptozocin, tamoxifen, taxanes, taxol, testosterone propionate, thalidomide, thioguanine, thiotepa, uracil mustard, vinblastine, and vincristine.

37. The method of claim 33, wherein said therapeutic agent is a cytokine selected from the group consisting of interleukin-1 (IL-1), IL-2, IL-3, IL-6, IL-10, IL-12, interferon-alpha, interferon-beta, and interferon-gamma.

38. The method of claim 33, wherein said therapeutic agent is a colony-stimulating growth factor selected from the group consisting of granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), erythropoietin and thrombopoietin.

39. A method of treating a neoplastic disorder in a subject, comprising administering to said subject a "naked" polyvalent protein complex according to claim 1, wherein at least one of said antigen binding sites binds to an antigen selected from the group consisting of alpha fetoprotein, A3, CA125, carcinoembryonic antigen (CEA), CD19, CD20, CD21, CD22, CD23, CD30, CD33, CD45, CD74, CD80, colon-specific antigen-p (CSAp), EGFR, EGP-1, EGP-2, folate receptor, HER2/neu, HLA-DR, human chorionic gonadotropin, Ia, IL-2, IL-6, insulin-like growth factor, KS-1, Le(y), MAGE, MUC1, MUC2, MUC3, MUC4, NCA66, necrosis antigens, PAM-4, placental growth factor, prostatic acid phosphatase PSA, PSMA, S100, T101, TAC, TAG-72, tenascin and VEGF.

40. The method of claim 39 , wherein the neoplastic disorder is selected from the group consisting of carcinomas, sarcomas, gliomas, lymphomas, leukemias, and melanomas.

41. A method for treating a B-cell malignancy, or B-cell immune or autoimmune disorder in a subject, comprising administering to said subject one or more dosages of a therapeutic composition comprising a polyvalent protein complex of claim 1 and a pharmaceutically acceptable carrier.

42. A method for treating a B-cell malignancy, or B-cell immune or autoimmune disorder in a subject, comprising administering to said subject one or more dosages of a therapeutic composition comprising a polyvalent protein complex of claim 2 and a pharmaceutically acceptable carrier, wherein each antigen binding site binds a distinct epitope of CD19, CD20 or CD22.

43. The method of claim 42, wherein said polyvalent protein complex is parenterally administered in a dosage of 20 to 1500 milligrams protein per dose.

44. The method of claim 42, wherein said polyvalent protein complex is parenterally administered in a dosage of 20 to 500 milligrams protein per dose.

45. The method of claim 42, wherein said polyvalent protein complex is parenterally administered in a dosage of 20 to 100 milligrams protein per dose.

46. The method of claim 42, wherein said subject receives the polyvalent protein complex as repeated parenteral dosages of 20 to 100 milligrams protein per dose.

47. The method of claim 42, wherein said subject receives the polyvalent protein complex as repeated parenteral dosages of 20 to 1500 milligrams protein per dose.

48. The method of claim 42, wherein a sub-fraction of the polyvalent protein complex is labeled with a radioactive isotope.

49. The method of claim 48, wherein said radioactive isotope is selected from the group consisting of  $^{32}\text{P}$ ,  $^{33}\text{P}$ ,  $^{47}\text{Sc}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{67}\text{Ga}$ ,  $^{90}\text{Y}$ ,  $^{111}\text{Ag}$ ,  $^{111}\text{In}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{142}\text{Pr}$ ,  $^{153}\text{Sm}$ ,  $^{161}\text{Tb}$ ,  $^{166}\text{Dy}$ ,  $^{166}\text{Ho}$ ,  $^{177}\text{Lu}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{189}\text{Re}$ ,  $^{212}\text{Pb}$ ,  $^{212}\text{Bi}$ ,  $^{213}\text{Bi}$ ,  $^{211}\text{At}$ ,  $^{223}\text{Ra}$  and  $^{225}\text{Ac}$  or a combination thereof.

50. A method for detecting or diagnosing a B-cell malignancy, or B-cell immune or autoimmune disorder in a subject, comprising administering to said subject a diagnostic composition comprising a polyvalent protein complex of claim 2 and a pharmaceutically acceptable carrier, wherein each antigen binding site binds a distinct epitope of CD19, CD20 or CD22, and wherein said complex is radiolabeled with a radionuclide selected from the group consisting of  $^{18}\text{F}$ ,  $^{52}\text{Fe}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{86}\text{Y}$ ,  $^{89}\text{Zr}$ ,  $^{94\text{m}}\text{Tc}$ ,  $^{94}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{154-158}\text{Gd}$ ,  $^{177}\text{Lu}$ ,  $^{32}\text{P}$ ,  $^{188}\text{Re}$ , and  $^{90}\text{Y}$  or a combination thereof.

51. The method of claim 50, wherein said radioactive labels are imaged using computed tomography (CT), single photon emission computed tomography (SPECT), or positron emission tomography (PET).

52. The method of claim 50, wherein the application is for intraoperative diagnosis to identify occult neoplastic tumors.

53. A method for detecting or diagnosing a B-cell malignancy, or B-cell immune or autoimmune disorder in a subject, comprising administering to said subject a diagnostic composition comprising a polyvalent protein complex of claim 2 and a pharmaceutically acceptable carrier, wherein each antigen binding site binds a distinct epitope of CD19, CD20 or CD22, and wherein said complex is labeled with one or more image enhancing agents for use in magnetic resonance imaging (MRI).

54. The method of claim 53, wherein said image enhancing agent is a paramagnetic ion selected from the group consisting of chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), vanadium (II), terbium (III), dysprosium (III), holmium (III) and erbium (III).



55. A method of diagnosing a non-neoplastic disease or disorder, comprising administering to a subject suffering from said disease or disorder a complex according to claim 1, wherein a detectable label is attached to said complex, and wherein one or more of said antigen binding sites is specific for a marker substance of the disease or disorder.

56. The method of claim 55, wherein said disease or disorder is caused by a fungus.

57. The method of claim 56, wherein said fungus is selected from the group consisting of *Microsporum*, *Trichophyton*, *Epidermophyton*, *Sporothrix schenckii*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Candida albicans*.

58. The method of claim 55 wherein said disease or disorder is caused by a virus.

59. The method of claim 58, wherein said virus is selected from the group consisting of human immunodeficiency virus (HIV), herpes virus, cytomegalovirus, rabies virus, influenza virus, hepatitis B virus, Sendai virus, feline leukemia virus, Reo virus, polio virus, human serum parvo-like virus, simian virus 40, respiratory syncytial virus, mouse mammary tumor virus, Varicella-Zoster virus, Dengue virus, rubella virus, measles virus, adenovirus, human T-cell leukemia viruses, Epstein-Barr virus, murine leukemia virus, mumps virus, vesicular stomatitis virus, Sindbis virus, lymphocytic choriomeningitis virus, wart virus and blue tongue virus.

60. The method of claim 55 wherein said disease or disorder is caused by a bacterium.

61. The method of claim 60, wherein said bacterium is selected from the group consisting of *Anthrax bacillus*, *Streptococcus agalactiae*, *Legionella pneumophila*, *Streptococcus pyogenes*, *Escherichia coli*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pneumococcus*, *Hemophilis influenzae B*, *Treponema*

pallidum, Lyme disease spirochetes, *Pseudomonas aeruginosa*, *Mycobacterium leprae*, *Brucella abortus*, and *Mycobacterium tuberculosis*

62. The method of claim 55 wherein said disease or disorder is caused by a *Mycoplasma*.

63. The method of claim 55 wherein said disease or disorder is caused by a parasite.

64. The method of claim 55 wherein said disease or disorder is malaria.

65. The method of claim 55, wherein said disease or disorder is an autoimmune disease.

66. The method of claim 65, wherein said autoimmune disease is selected from the group consisting of acute idiopathic thrombocytopenic purpura, chronic idiopathic thrombocytopenic purpura, dermatomyositis, Sydenham's chorea, myasthenia gravis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, polyglandular syndromes, bullous pemphigoid, diabetes mellitus, Henoch-Schonlein purpura, post-streptococcal nephritis, erythema nodosum, Takayasu's arteritis, Addison's disease, rheumatoid arthritis, multiple sclerosis, sarcoidosis, ulcerative colitis, erythema multiforme, IgA nephropathy, polyarteritis nodosa, ankylosing spondylitis, Goodpasture's syndrome, thromboangitis obliterans, Sjogren's syndrome, primary biliary cirrhosis, Hashimoto's thyroiditis, thyrotoxicosis, scleroderma, chronic active hepatitis, polymyositis/dermatomyositis, polychondritis, paronychia, Wegener's granulomatosis, membranous nephropathy, amyotrophic lateral sclerosis, tabes dorsalis, giant cell arteritis/polymyalgia, pernicious anemia, rapidly progressive glomerulonephritis, psoriasis, and fibrosing alveolitis.

67. The method of claim 55, wherein said the disease or disorder is myocardial infarction, ischemic heart disease, or atherosclerotic plaques.

68. The method of claim 55, wherein said disease or disorder is graft rejection.

69. The method of claim 55, wherein said disease or disorder is Alzheimer's disease.

70. The method of claim 55, wherein said disease or disorder is caused by atopic tissue.

71. The method of claim 55, wherein said disease or disorder is inflammation caused by accretion of activated granulocytes, monocytes, lymphoid cells or macrophages at the site of inflammation, and wherein the inflammation is caused by an infectious agent.

72. The method of claim 55, wherein said detectable label is a radionuclide selected from the group consisting of  $^{18}\text{F}$ ,  $^{52}\text{Fe}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{86}\text{Y}$ ,  $^{89}\text{Zr}$ ,  $^{94\text{m}}\text{Tc}$ ,  $^{94}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{154-158}\text{Gd}$ ,  $^{177}\text{Lu}$ ,  $^{32}\text{P}$ ,  $^{188}\text{Re}$ , and  $^{90}\text{Y}$  or a combination thereof.

73. The method of claim 72, wherein said radioactive labels are imaged using computed tomography (CT), single photon emission computed tomography (SPECT), or positron emission tomography (PET).

74. The method of claim 73, wherein the application is for intraoperative diagnosis of said disease or disorder.

75. The method of claim 55, wherein at least one of said antigen binding sites is specific for a targetable construct, and wherein said construct comprises one or more image enhancing agents for use in magnetic resonance imaging (MRI).

76. The method of claim 75, wherein said image enhancing agent is a paramagnetic ion selected from the group consisting of chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), vanadium (II), terbium (III), dysprosium (III), holmium (III) and erbium (III).

77. The method of claim 55, wherein at least one of said antigen binding sites is specific for a targetable construct, and wherein said targetable construct comprises one or more image enhancing agents for use in ultrasound imaging.

78. The method of claim 55, wherein at least one of said antigen binding sites is specific for a targetable construct and wherein said targetable construct comprises a liposome with a bivalent HSG-peptide covalently attached to the outside surface of the liposome lipid membrane.

79. The method of claim 74, wherein said liposome is gas filled.

80. A pretargeting method of treating or diagnosing a non-neoplastic disease or disorder in a subject comprising

(a) administering to said subject the polyvalent protein complex of claim 1, wherein two antigen binding sites are directed to a marker substance, or marker substances specific for the disorder, and one antigen binding sites is directed to a targetable construct comprising a bivalent hapten;

(b) optionally administering to said subject a clearing composition, and allowing said composition to clear the polyvalent complex from circulation; and

(c) administering to said subject said targetable construct comprising a bivalent hapten, wherein the targetable construct further comprises one or more chelated or chemically bound therapeutic or diagnostic agents.

81. The method of claim 80, wherein said disease or disorder is caused by a fungus.

82. The method of claim 81, wherein the species of fungus is selected from the group consisting of *Microsporum*, *Trichophyton*, *Epidermophyton*, *Sporothrix schenckii*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, or *Candida albicans*.

83. The method of claim 80 wherein said disease or disorder is caused by a virus.

84. The method of claim 83, wherein the species of virus is selected from the group consisting of human immunodeficiency virus (HIV), herpes virus, cytomegalovirus, rabies virus, influenza virus, hepatitis B virus, Sendai virus, feline leukemia virus, Reo virus, polio virus, human serum parvo-like virus, simian virus 40, respiratory syncytial virus, mouse mammary tumor virus, Varicella-Zoster virus, Dengue virus, rubella virus, measles virus, adenovirus, human T-cell leukemia viruses, Epstein-Barr virus, murine leukemia virus, mumps virus, vesicular stomatitis virus, Sindbis virus, lymphocytic choriomeningitis virus, wart virus and blue tongue virus.

85. The method of claim 80 wherein said disease or disorder is caused by a bacterium.

86. The method of claim 85, wherein the bacterium is selected from the group consisting of Anthrax bacillus, Streptococcus agalactiae, Legionella pneumophila, Streptococcus pyogenes, Escherichia coli, Neisseria gonorrhoeae, Neisseria meningitidis, Pneumococcus, Hemophilis influenzae B, Treponema pallidum, Lyme disease spirochetes, Pseudomonas aeruginosa, Mycobacterium leprae, Brucella abortus, and Mycobacterium tuberculosis.

87. The method of claim 80 wherein said disease or disorder is caused by a Mycoplasma.

88. The method of claim 80 wherein said disease or disorder is caused by a parasite.

89. The method of claim 80 wherein the disease or disorder is malaria.

90. The method of claim 80, wherein said disease or disorder is an autoimmune disease.

91. The method of claim 90, wherein the autoimmune disease is selected from the group consisting of acute idiopathic thrombocytopenic purpura, chronic idiopathic thrombocytopenic purpura, dermatomyositis, Sydenham's chorea,

myasthenia gravis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, polyglandular syndromes, bullous pemphigoid, diabetes mellitus, Henoch-Schonlein purpura, post-streptococcal nephritis, erythema nodosum, Takayasu's arteritis, Addison's disease, rheumatoid arthritis, multiple sclerosis, sarcoidosis, ulcerative colitis, erythema multiforme, IgA nephropathy, polyarteritis nodosa, ankylosing spondylitis, Goodpasture's syndrome, thromboangitis obliterans, Sjogren's syndrome, primary biliary cirrhosis, Hashimoto's thyroiditis, thyrotoxicosis, scleroderma, chronic active hepatitis, polymyositis/dermatomyositis, polychondritis, paronychia, Wegener's granulomatosis, membranous nephropathy, amyotrophic lateral sclerosis, tabes dorsalis, giant cell arteritis/polymyalgia, pernicious anemia, rapidly progressive glomerulonephritis, psoriasis, and fibrosing alveolitis.

92. The method of claim 80, wherein the disease or disorder is selected from the group consisting of myocardial infarction, ischemic heart disease, and atherosclerotic plaques.

93. The method of claim 80, wherein the disease or disorder is graft rejection.

94. The method of claim 80, wherein the disease or disorder is Alzheimer's disease.

95. The method of claim 80, wherein the disease or disorder is caused by atopic tissue.

96. The method of claim 80, wherein the disease or disorder is inflammation caused by accretion of activated granulocytes, monocytes, lymphoid cells or macrophages at the site of inflammation, and wherein the inflammation is caused by an infectious agent.

97. The method of claim 80, wherein said targetable construct is labeled with a radionuclide selected from the group consisting of  $^{18}\text{F}$ ,  $^{52}\text{Fe}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{86}\text{Y}$ ,  $^{89}\text{Zr}$ ,  $^{94\text{m}}\text{Tc}$ ,  $^{94}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{154-158}\text{Gd}$ ,  $^{177}\text{Lu}$ ,  $^{32}\text{P}$ ,  $^{188}\text{Re}$ , and  $^{90}\text{Y}$  or a combination thereof.

98. The method of claim 97, wherein said radioactive labels are imaged using computed tomography (CT), single photon emission computed tomography (SPECT), or positron emission tomography (PET).

99. The method of claim 97, wherein the application is for intraoperative diagnosis of the disorder.

100. The method of claim 80, wherein said targetable construct comprises one or more image enhancing agents for use in magnetic resonance imaging (MRI).

101. The method of claim 100, wherein image enhancing agent is a paramagnetic ion selected from the group consisting of chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), vanadium (II), terbium (III), dysprosium (III), holmium (III) and erbium (III).

102. The method of claim 80, wherein said targetable construct comprises one or more image enhancing agents for use in ultrasound imaging.

103. The method of claim 102, wherein said targetable construct is a liposome with a bivalent HSG-peptide covalently attached to the outside surface of the liposome lipid membrane.

104. The method of claim 103, wherein said liposome is gas filled.

105. A method of antibody dependent enzyme prodrug therapy (ADEPT) comprising;

(a) administering to a patient with a neoplastic disorder the polyvalent protein complex of claim 3, wherein said complex comprises a covalently attached enzyme capable of activating a prodrug,

(b) optionally administering to said subject a clearing composition, and allowing said composition to clear the polyvalent complex from circulation, and

(c) administering said prodrug to the patient.

106. An assay method comprising detecting a target molecule using one or more polyvalent protein complexes of claim 1.

107. An immunostaining method comprising staining a cell using one or more polyvalent protein complexes of claim 1.

108. An isolated nucleic acid molecule encoding a first or second polypeptide according to claim 1.

109. A nucleic acid expression cassette comprising the isolated nucleic acid of claim 108.

110. An episome comprising:

(a) a first promoter operationally connected to a first nucleic acid encoding a first polypeptide comprising a polypeptide chain represented by the formula  $a_1-l_1-a_2-l_2-a_3$ , wherein  $a_1$ ,  $a_2$ , and  $a_3$  are immunoglobulin variable domains and  $l_1$  and  $l_2$  are peptide linkers,

(b) a second promoter operationally connected to a second nucleic acid encoding a polypeptide comprising a second polypeptide chain represented by the formula  $b_1-l_3-b_2-l_4-b_3$ , wherein  $b_1$ ,  $b_2$ , and  $b_3$  are immunoglobulin variable domains and  $l_3$  and  $l_4$  are peptide linkers,

wherein said first and second polypeptide chain together form a complex comprising at least three antigen binding sites,

wherein each of said antigen binding sites comprises a variable domain from said first polypeptide chain and a variable domain from said second polypeptide chain,

wherein said first nucleic acid and said second nucleic acid are coexpressed when the episome is transformed into a host cell.

111. The episome of claim 110 which is a plasmid or a cosmid.

112. A host cell comprising an episome according to claim 110.



113. The host cell of claim 112, wherein said host cell is selected from the group consisting of *E. coli*, yeast, a plant cell and a mammalian cell.

114. A method of preparing a polyvalent protein complex, comprising culturing a host cell according to claim 112.

115. The host cell of claim 112, wherein said cell is a murine myeloma cell line.

116. The episome of claim 111, wherein the plasmid is pdHL2.